Drug discovery for chagas disease: A viewpoint

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ABSTRACT

Chagas disease is a neglected tropical disease caused by the protozoan parasite Trypanosoma cruzi. It is a significant public health problem, affecting millions of people worldwide. And although it was described 110 years ago, only two old nitroheterocyclic drugs, benznidazole and nifurtimox, are currently available for the treatment of Chagas disease and both have several limitations. Besides the clear unmet medical need, many challenges preclude the development of new treatments, some of them related to a lack of understanding of the pathophysiology of the disease and parasite-host interactions. New knowledge and tools are becoming available, but the number of new chemical entities progressing through the preclinical pipeline is inadequate. Therefore, it is still uncertain whether safe, effective and accessible new drugs will be available in the near future. The Chagas disease research community must commit to even greater collaboration to ensure that patients eventually benefit from better treatments.

1. Introduction

Chagas disease (CD), or American trypanosomiasis, is a neglected tropical disease (NTD) caused by the protozoan parasite Trypanosoma cruzi. Infection occurs by vectorial, congenital, iatrogenic or oral routes, and the disease is characterized by two distinct clinical phases. CD begins with an acute phase with detectable parasitaemia, usually asymptomatic and undiagnosed, followed by a lifelong chronic phase which can manifest as a variety of debilitating conditions. The chronic phase is divided into chronic asymptomatic or indeterminate (characterized by seropositivity for T. cruzi and absence of clinical signs), and chronic symptomatic (encompassing around 30% of patients) (Pérez-Molina and Molina, 2017; World Health Organization, 2012).

An estimated 6–7 million people are infected with T. cruzi worldwide. CD is considered to be the parasitic disease with the greatest socioeconomic impact in Latin America, causing over 800,000 disability-adjusted life years and around 7500 deaths per year (Lee et al., 2013; World Health Organization, 2012). It is important to acknowledge that both the number of new cases and the burden of CD in Latin America have decreased substantially over recent years, mostly due to the control of transmission by the vector and by transfusion (World Health Organization, 2017).

However, the profile of CD has changed from a disease primarily impacting rural areas of Latin America to a public health concern in large cities, and in the United States, Canada, Europe, and elsewhere (Briceno-Leon, 2009; Gascon et al., 2010). Several challenges remain, such as poor access to diagnostics, the lack of timely tools to assess parasitological cure, and the suboptimal profile of antitypanosomal drugs, which require extended treatment durations, have side effects and are unable to eliminate all parasites in some patients (Chatelain, 2014; Dias et al., 2016; World Health Organization, 2012).

There is, therefore, a clear need for safe, effective, and accessible new therapies for CD. In this short review, the current status and challenges associated with drug discovery for CD are discussed. It provides a personal viewpoint based on multiple discussions and collaborations with scientists from the Chagas community around the globe.

2. Available drugs for Chagas disease

According to the World Health Organization (WHO), the goal of treatment for CD is to eliminate the parasite from infected individuals, thus decreasing the probability of developing symptomatic CD and hindering parasite transmission (World Health Organization, 2012).

Only two old nitroheterocyclic drugs, benznidazole (BZN) and nifurtimox (NFX) (Fig. 1), are available for the treatment of CD. They require prolonged treatment (60–90 days) and are primarily considered effective for acute infections (including neonates or infants with congenital transmission), cases of reactivation during the chronic phase, chronic patients up to 18 years old, and infected women of childbearing age (administered concomitantly with contraceptive measures) (Kratz et al., 2018).
Treatment of patients with BZN has a very clear trypanocidal effect, drastically reducing parasitaemia in both acute and chronic phases, but in some cases, parasites persist and patients test positive for infection in a subsequent screen (e.g. testing by PCR). In the adult population, seroconversion (the decisive marker of parasite clearance) can take years to decades after treatment, making it difficult to establish a “proof of cure” in this population (Chatelain, 2017; Kratz et al., 2018; Morillo et al., 2015; Torrico et al., 2018).

Thus, the efficacy of BZN in the chronic indeterminate adult population, and its potential to preclude the development of cardiomyopathies or gastrointestinal pathologies, are still a matter of intense debate (Chatelain, 2017; Morillo et al., 2015). There is a growing body of evidence, mostly from observational studies, that both BZN and NFX reduce morbidity and mortality when administered to adults with chronic CD (Cardoso et al., 2018; Fabbro et al., 2007; Viotti et al., 2006). Therefore, WHO recommends the treatment be offered to chronically infected patients (Dias et al., 2016; Pan American Health Organization, 2019; Kratz et al., 2018; World Health Organization, 2012).

In addition to inadequate efficacy, the current drugs for CD have several other limitations that substantially restrict their use. Their supply is insufficient, both are contraindicated during pregnancy due to genotoxic effects, and treatment produces adverse effects, mostly cutaneous (BZN) and gastrointestinal (NFX), with treatment discontinuation rates typically ranging from 15 to 20% (Kratz et al., 2018; Molina et al., 2015; Morillo et al., 2015).

3. Drug discovery pipeline

Drug discovery for NTDs is a very demanding field, and the challenges associated with it have recently been reviewed in several publications (Burrows et al., 2014; De Rycker et al., 2018; Field et al., 2017; Rao et al., 2019). CD drug discovery scientists face many particular challenges, mainly linked to the variety of unanswered questions regarding both the disease itself and parasite-host interactions. The recent disappointing results of clinical trials evaluating CYP51 inhibitors (azoles targeting T. cruzi ergosterol synthesis pathway) – posaconazole (Molina et al., 2014) and fosravuconazole (Torrico et al., 2018) – highlight the colossal challenge of drug discovery for kinetoplastid diseases.

Although CD was described 110 years ago by the Brazilian researcher Carlos Chagas, little is known about the factors influencing the progression of the disease and the development of clinical manifestations. Ultimately, for drug discovery campaigns, it is still unclear what role immune response and parasite reactivation play in the severity of the disease, and whether complete parasite clearance after trypanocidal treatment will eventually lead to clinical benefits for indeterminate chronic CD patients (Chatelain, 2017; Rao et al., 2019).

Nevertheless, chemotherapy with trypanocidal drugs remains the foundation of all CD therapeutic strategies. To guide the development of new treatments (either new chemical entities or improved regimens of current drugs), it is fundamental to define a clear target product profile (TPP), which describes the features required for the ideal final product. In the case of new chemical entities, the TPP will also orient the construction of screening cascades and the definition of compound progression criteria (and eventually a target candidate profile – TCP) used during early drug discovery. Several experts in the field have recently published a TPP for CD (Rao et al., 2019), and another has been developed by DNDi (Table 1) (Chatelain, 2014).

The first step of every drug discovery campaign is the identification of chemical starting points (i.e. hit compounds) via screening of chemical libraries using either target-based or phenotypic-based approaches. In the NTD field, target-based programs are scarce due to very few validated targets and the persistent gap between genetic and chemical validation in trypanosomatis (Gilbert, 2013). Phenotypic- or cell-based approaches remain the main focus for CD drug discovery, and several assays have been described in the literature (Chatelain and Ioset, 2018). Numerous compounds that have been identified using this strategy have been recently reviewed (Scrim et al., 2018). Unfortunately, very few of them have progressed through lead optimization into preclinical and/or clinical development.

In fact, the number of compounds currently in the later stages of the preclinical pipeline is modest and represents only a few chemical classes, such as nitroimidazoles (fexinidazole recently registered for sleeping sickness and currently in Phase II clinical trials for CD), and the pan-kinetoplastids benzoazaboroles (exemplified by AN4169/SCYX6759) and proteasome inhibitors (exemplified by GNF6702) (Fig. 1) (DNDi Portfolio, 2019; Khare et al., 2016; Moraes et al., 2014).

4. New tools and strategies

In order to improve the translation of current models used for CD drug discovery, the research community must ensure there is a continuous effort to understand T. cruzi biology and CD pathophysiology, while in parallel new and better tools are developed based on the knowledge acquired. This synergistic approach is likely to generate

![Fig. 1. Benchmark drugs benznidazole and nifurtimox, and representatives of new chemical classes under development for Chagas disease.](image-url)
opportunities that could accelerate the development of a new chemotherapeutic for CD.

The impact of the information gathered during the investigation of the failure of CYP51 inhibitors in Phase II trials is a classic example of positive feedback from the clinical setting into early drug discovery. New improved *in vitro* assays, including panels of *T. cruzi* strains and clinical isolates (covering all current discrete typing units, which allows the assessment of parasite genetic diversity to some extent), time-kill and prolonged washout assays (which allow the differentiation between nitroaromatic drugs and posaconazole), and CYP51 inhibition assays are now part of screening cascades used to prioritize only the most promising compounds (able to produce sterile *in vitro* cure) to be progressed into *in vivo* experiments (Cal et al., 2016; Chatelain and Ioset, 2018; MacLean et al., 2018; Moraes et al., 2014).

Additionally, transgenic parasites and bioluminescent imaging techniques allow the live monitoring of parasitism in mice and have facilitated the development of new stringent murine models that can also differentiate between B2N and posaconazole and might show better translatable (Chatelain and Konar, 2015; Costa et al., 2018; Lewis et al., 2014). Systematic improvement and validation of Chagas models in higher order mammals, such as dogs or non-human primates, that more closely reflect the human disease (Diniz et al., 2010; Guedes et al., 2002; Rosner et al., 1988), is highly desirable. The combination of different animal models might allow a better understanding of parasite tissue tropism, establishment of PK/PD relationships (one of the main hurdles in CD drug discovery), and determination of immunological responses to treatment, and, in theory, improve the predictability of drug candidate efficacy (Chatelain and Konar, 2015).

A dormant form of *T. cruzi* was recently identified (Sánchez-Valdés et al., 2018). These non-replicating forms persist after treatment with B2N (up to 30 days) and might help to explain the variability in the efficacy of current drugs, which are typically highly effective in reducing parasitemia but show variable rates of seroconversion and conversion to negative PCR (Kratz et al., 2018; Morillo et al., 2015; Yun et al., 2009). New tools that would allow screening of compounds against “persistent” forms are highly desirable but may prove difficult to achieve, and their feasibility has yet to be assessed.

The identification of new molecular targets, via target discovery using genetic approaches and/or via target deconvolution of phenotypic hits, can also have a positive impact in CD drug discovery. The use of target-based approaches in combination with modern drug discovery technologies, such as DNA encoded libraries (Neri, 2017) and ultra-large *in silico* screenings (Lyu et al., 2019), might enable the assessment of targets druggability and the identification of novel chemotypes in a larger scale, and in parallel provide additional tools for their optimization into preclinical and clinical candidates.

Other approaches that are consolidated and/or expanding in other therapeutic areas might also play a key future role in CD drug discovery, including prophylactic and therapeutic vaccines (Beaumier et al., 2016; Portillo et al., 2019), drug combinations (Ashley and Phyo, 2018; Tyers and Wright, 2019), immunomodulation and adjunct therapies (DNDi Portfolio, 2019; Pahaljani et al., 2016), and covalent inhibitors (Ghosh et al., 2019).

### 5. Conclusion

In view of recent progress and the remaining challenges associated with CD drug discovery, the likelihood of a new optimal treatment for CD arising in the next few years remains uncertain. Nonetheless, it is clear that the success of a drug discovery enterprise does not depend solely on the implementation of new tools and technologies, but also on the availability of robust funding and collaborative R&D models, and a better understanding of the pathophysiology of the disease (Chatelain, 2017; Chatelain and Ioset, 2011; Ferrins and Pollastri, 2018; Purdott et al., 2014; Rao et al., 2019). Therefore, the Chagas community must continuously advocate for even greater support and collaboration, and keep progressing drug discovery projects (with new chemical series and complementary approaches) in parallel with a large-scale collective effort to answer basic questions about CD.

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### Declaration of Competing Interest

The author is an employee of DNDi. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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**Table 1**

DNDi's Chagas disease Target Product Profile (TPP).

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>Chronic</td>
<td>Chronic and Acute (Reactivation)</td>
</tr>
<tr>
<td><strong>Strains</strong></td>
<td>Tcl, TclI, TeV and TclVI*</td>
<td>All*</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>All areas</td>
<td>All</td>
</tr>
<tr>
<td><strong>Adult / Children</strong></td>
<td>Adult</td>
<td>All Superiority to benznidazole in different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td><strong>Clinical efficacy</strong></td>
<td>Non-inferior to benznidazole in all endemic regions (parasitological)</td>
<td>Superiority to benznidazole or nifurtimox</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>3 CE plus 2 standard LE or ECG during treatment</td>
<td>No CE or LE or ECG needed during treatment</td>
</tr>
<tr>
<td><strong>Activity against resistant strains</strong></td>
<td>Not necessary</td>
<td>Active against nitrofuran- and nitroimidazole-resistant <em>T. cruzi</em> strains</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy / Lactation</td>
<td>None</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>No genotoxicity; No proarrhythmic potential</td>
<td>No genotoxicity; No teratogenicity; No negative isotropic effect; No proarrhythmic potential</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>No clinically significant interaction with anti-hypertensive, anti-</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>arrhythmic and anti-coagulants drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>3 years, climatic zone IV</td>
<td>5 years, climatic zone IV</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Comparable to systemic antifungal treatments</td>
<td>Once daily / 30 days</td>
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</tbody>
</table>

* Classification according to (Zingales et al., 2009); requires further research for definition of target strains for evaluation.

* CE, clinical evaluation; LE, laboratory evaluation; ECG, electrocardiogram.


